NOVARTIS

Methergin®

Composition
Active substance
Methylergometrine maleate

Excipients
Coated tablets: Lactose, tableting excipients.
Solution for injection: Sodium chloride, water.

Pharmaceutical form and quantity of active substance per unit
Each coated tablet contains 0.125 mg methylergometrine maleate.
Each 1 ml ampoule of solution for injection contains 0.2 mg methylergometrine maleate.

Indications/Potential uses
Active management of the third stage of labour (to promote separation of the placenta and reduce blood loss).
Treatment of uterine atony/haemorrhage during and after the third stage of labour; in association with Caesarean section; following abortion.
Treatment of subinvolution of the uterus, lochiometra and puerperal bleeding.

Dosage and Administration
Standard dosage
Active management of the third stage of labour
The recommended route of administration for Methergin is intramuscular (i.m.) injection. When administering Methergin intravenously (i.v.), the dose must be injected slowly over at least 60 seconds (see **Warnings and Precautions**). The recommended dose for Methergin is: 1 ml (0.2 mg) i.m. or 0.5-1 ml (0.1-0.2 mg) slowly i.v. following delivery of the anterior shoulder or, at the latest, immediately after delivery of the infant. Expulsion of the placenta – usually separated by the first strong uterine contraction following administration of Methergin – should be manually assisted by applying fundal pressure.
The recommended dose for delivery under general anaesthesia is 1 ml (0.2 mg) by slow intravenous injection.

Uterine atony/haemorrhage
The recommended route of administration for Methergin is intramuscular (i.m.) injection. When administering Methergin intravenously (i.v.), the dose must be injected slowly over at least 60 seconds (see **Warnings and Precautions**).
The recommended dose is: 1 ml (0.2 mg) i.m. or 0.5-1 ml (0.1-0.2 mg) i.v. This dose may be repeated as required at intervals of no less than 2 hours, although no more than 5 injections should be given during a 24-hour period.
Subinvolution of the uterus, lochiometra, puerperal bleeding
The recommended dose for Methergin is: 1-2 tablets (0.125-0.25 mg) orally or 0.5-1 ml (0.1-0.2 mg) s.c. or i.m. up to 3 times daily, normally for a maximum of 5 days.
Special dosage recommendations
Renal/hepatic impairment
Caution is required when administering Methergin to patients with impaired hepatic or renal function (see **Warnings and Precautions**).

Contraindications
Pregnancy; first stage of labour, second stage of labour before delivery of the anterior shoulder (Methergin must not be used for induction of labour or in uterine inertia); severe hypertension, pre-eclampsia, eclampsia; arterial occlusive disease (including ischaemic heart disease); sepsis; known hypersensitivity to methylergometrine, other ergot alkaloids or any of the other ingredients of Methergin; hepatic and renal impairment.

Warnings and Precautions
General administration recommendations
In breech and other abnormal presentations, Methergin should not be given until immediately after delivery of the infant, and it should not be given in multiple birth before the last infant has been delivered.
Active management of the third stage of labour requires medical supervision.
The recommended route of administration is intramuscular injection. Intravenous injections should be given slowly over a period of no less than 60 seconds and with careful monitoring of blood pressure. Intra- or periarterial injection must be avoided.

Lactation
In view of possible adverse effects on the infant and reduced milk secretion, use of Methergin during lactation is not recommended. Mothers should not breastfeed during treatment with Methergin and for at least 12 hours after the final dose. Milk secreted during this period should not be given to the infant (see **Pregnancy and Lactation**).

Hypertension and hepatic or renal impairment
Caution is required in the presence of mild to moderate hypertension (severe hypertension is a contraindication) and hepatic or renal impairment.

Lactose
Methergin tablets contain lactose (40.9 mg/tablet). Patients with rare hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Methergin tablets.

Coronary heart disease
Patients with coronary heart disease or risk factors for coronary heart disease (e.g. smoking, obesity, diabetes, high cholesterol levels) are more likely to develop myocardial ischaemia or infarction in association with methylergometrine-induced vasospasm (see **Adverse effects**).
Caution is required in the presence of anaemia or severe hyperthyroidism because of possible aggravation of cardiovascular symptoms.
Caution is required when coadministering sulprostone and/or oxytocin in the treatment of postpartum atonic uterine haemorrhage (see **Interactions**).

Mismedication
There have been reports of accidental administration of Methergin to neonates. Symptoms observed in these cases of neonatal overdosage included respiratory depression, convulsions, cyanosis and oliguria. Symptomatic treatment is recommended; respiratory and cardiovascular supportive measures may be required in severe cases. Fatalities have been reported in the absence of adequate treatment (see **Overdose**).

Interactions
Ergot alkaloids are CYP3A4 substrates.

CYP3A4 inhibitors
Concomitant use of Methergin with potent CYP3A inhibitors such as macrolide antibiotics (e.g. troleandomycin, erythromycin, clarithromycin), HIV protease inhibitors or reverse transcriptase inhibitors (e.g. ritonavir, indinavir, nelfinavir, delavirdine) or azole antifungals (e.g. ketoconazole, itraconazole, voriconazole) should be avoided since it can lead to elevated exposure to methylergometrine and thus to ergot toxicity (vasospasm and ischaemia of the extremities and other tissues).

Bromocriptine
Coadministration of Methergin with bromocriptine during the puerperium is not recommended because methylergometrine may increase the vasoconstrictor effect of ergot alkaloids.

Prostaglandins
Prostaglandins (e.g. sulprostone, dinoprostone, misoprostol) facilitate myometrial contraction, and Methergin may therefore enhance the function of prostaglandins in the uterus and *vice versa*. Coadministration of these drugs is not recommended.

Less potent CYP3A4 inhibitors
Caution is required when combining Methergin with less potent CYP3A inhibitors (e.g. cimetidine, delavirdine, grapefruit juice, quinupristin, dalfopristin) as this may result in increased exposure to methylergometrine.

Vasoconstrictors, triptans, sympathomimetics and other ergot alkaloids
Caution is required when Methergin is used concurrently with other vasoconstrictors or other ergot alkaloids.
Methylergometrine may increase the vasoconstrictor/vasopressor effects of other drugs, such as triptans ($5HT_{1B/1D}$ receptor agonists), sympathomimetics (including those in local anaesthetics) or other ergot alkaloids.

Beta-blockers
Caution is required when using Methergin in combination with beta-blockers. Coadministration of beta-blockers may increase the vasoconstrictor effect of ergot alkaloids.

Anaesthetics
Anaesthetics such as halothane or methoxyflurane may reduce the uterotonic effect of Methergin (see **Dosage and Administration**).

CYP3A4 inducers
Drugs that are potent inducers of CYP3A4 (e.g. nevirapine, rifampicin[1]) may reduce the pharmacological effect of Methergin.

Glyceryl trinitrate and other antianginal drugs
Methylergometrine has vasoconstrictor activity and may reduce the effects of glyceryl trinitrate and other antianginal drugs.
For the prevention and treatment of uterine haemorrhage by i.m. injection, it may be advantageous to combine the two uterotonic agents, Methergin and oxytocin, since oxytocin has a very short latency period, while methylergometrine has a prolonged duration of action.
However, caution is required: There have been reports of sometimes fatal ventricular tachycardia/fibrillation and myocardial infarction/cardiac arrest in connection with coadministration of sulprostone and/or oxytocin and/or methylergometrine in the treatment of postpartum atonic uterine haemorrhage.

Pregnancy and Lactation
Pregnancy
There is clear evidence of risks to the human fetus. Methergin is contraindicated during pregnancy on account of its potent uterotonic effect, which increases the risk of abortion or premature contractions.

Lactation
Methergin passes into the breast milk (see **Pharmacokinetics**). There have been isolated reports of intoxication in breastfed infants whose mothers had been given Methergin over a period of several days.
One or more of the following symptoms were observed in breastfed infants (and disappeared on withdrawal of the medication): raised blood pressure, bradycardia or tachycardia, vomiting, diarrhoea, restlessness, convulsions.
Methergin may impair milk secretion.
On account of the risks of adverse effects in the infant and reduced milk secretion, use of Methergin during lactation is not recommended. Mothers should not breastfeed during treatment with Methergin and for at least 12 hours after the final dose. Milk secreted during this period should be discarded (see **Warnings and Precautions**).

Effects on ability to drive and use machines
Methylergometrine may cause light-headedness, dizziness and convulsions. Caution is therefore required when driving or operating machines.

Adverse effects
Frequency
Very common (> 1/10), common (> 1/100 to < 1/10), uncommon (> 1/1000 to < 1/100), rare (> 1/10 000 to < 1/1000), very rare (< 1/10 000)

Immune system disorders
Rare: Anaphylactic reactions (dyspnoea, hypertension, collapse, shock).

Nervous system disorders
Common: Headache.
Uncommon: Light-headedness, dizziness, convulsions.
Rare: Hallucinations.

Ear and labyrinth disorders
Very rare: Tinnitus.

Cardiac disorders
Uncommon: Chest pain.
Rare: Bradycardia, tachycardia, palpitations, myocardial infarction.
Very rare: Infarction due to coronary artery spasm.

Vascular disorders
Common: Hypertension.
Uncommon: Hypotension.
Rare: Vasoconstriction, vasospasm, arterial spasm.
Very rare: Thrombophlebitis.

Respiratory disorders
Very rare: Nasal congestion.

Gastrointestinal disorders
Uncommon: Nausea, vomiting.
Very rare: Diarrhoea.

Skin disorders
Common: Skin rash.
Uncommon: Hyperhidrosis.

Musculoskeletal disorders
Very rare: Muscle spasm.

Pregnancy, puerperium and perinatal conditions
Common: Abdominal pain (due to uterine contractions).

List of adverse effects from post-marketing spontaneous reports
The following adverse effects have been identified from post-marketing spontaneous reports. Because these reactions are voluntary reports from a population of uncertain size, it is not possible to reliably state their frequency.

Nervous system disorders
Stroke, paraesthesia.

Cardiac disorders
Ventricular fibrillation, ventricular tachycardia, angina pectoris, atrioventricular block.

Overdose
Signs and symptoms: Nausea, vomiting; hypertension or hypotension; numbness, tingling and pain in the extremities; respiratory depression; convulsions, coma.

Management: Elimination of orally ingested drug by repeated administration of high doses of activated charcoal.
Symptomatic treatment with strict cardiovascular and respiratory monitoring.
Benzodiazepines may be given if sedation is necessary.
In the event of severe arteriospasm, vasodilators should be administered (e.g. sodium nitroprusside, phentolamine or dihydralazine). In the event of coronary constriction, appropriate antianginal therapy (e.g. nitrates) should be given.

Mismedication
There have been reports of accidental administration of Methergin to neonates. Symptoms observed in these cases of neonatal overdosage included respiratory depression, convulsions, cyanosis and oliguria. Symptomatic treatment is recommended; respiratory and cardiovascular supportive measures may be required in severe cases. Fatalities have been reported in the absence of adequate treatment (see **Warnings and Precautions**).

Properties and Actions
ATC code: G02A B01

Mechanism of action/Pharmacodynamics
Methylergometrine, a semi-synthetic derivative of the naturally occurring alkaloid ergometrine, is a potent and specific uterotonic agent. It acts directly on uterine smooth muscle and increases the basal tone, frequency and amplitude of rhythmic contractions.
Compared with other ergot alkaloids its effect on the cardiovascular and central nervous systems is less pronounced. The strong and selective oxytocic effect of methylergometrine results from its specific pattern of actions as partial agonist and antagonist at serotoninergic, dopaminergic and alpha-adrenergic receptors. This does not entirely preclude vasoconstrictive complications, however (see **Adverse effects**).

Pharmacokinetics
Methylergometrine takes effect 30-60 seconds after intravenous administration, 2-5 minutes after intramuscular administration and 5-10 minutes after oral administration, and continues to act for 4-6 hours.

Absorption
Studies in fasting female volunteers showed oral absorption from a 0.2 mg methylergometrine tablet to be rapid, with a mean peak plasma concentration (C_{max}) of 3243 ± 1308 pg/ml observed at 1.12 ± 0.82 hours (t_{max}). Following i.m. injection of 0.2 mg, C_{max} was 5918 ± 1952 pg/ml and t_{max} was 0.41 ± 0.21 hours. The bioavailability of the tablets was equivalent to the i.m. solution and dose-proportional after 0.1 mg, 0.2 mg and 0.4 mg. Following i.m. injection the extent of absorption was approx. 25% greater than after oral administration. Delayed gastrointestinal absorption (t_{max} approx. 3 hours) was observed in postpartum women during continuous treatment with Methergin tablets.

Distribution
Following i.v. injection, methylergometrine is rapidly distributed from plasma to peripheral tissues (within 2-3 minutes or less). In female volunteers the volume of distribution is 56.1 ± 17.0 litres (about 0.5 litres/kg). It is not known whether the active substance crosses the blood-brain barrier.

Metabolism
Methylergometrine is metabolized mainly in the liver. The metabolic pathway has not been investigated in humans. *In vitro* studies showed N-demethylation and hydroxylation of the phenyl ring.

Elimination
In female volunteers plasma clearance after oral dosing is 14.4 ± 4.5 litres/hour, and mean elimination half-life 3.29 ± 1.31 hours. A study in male volunteers showed that only about 3% of an oral dose is excreted unchanged in the urine. The active substance is excreted mainly via the bile in the faeces. Methylergometrine is also excreted in milk. A milk-plasma ratio of 0.18 ± 0.03 was measured 1 hour after a single oral dose of 250 micrograms methylergometrine. The half-life of methylergometrine in milk is 2.3 ± 0.3 hours.

Preclinical data
Reproductive toxicity: No animal studies have been performed to assess the toxicity of Methergin on reproduction and fertility.

Mutagenicity and carcinogenic potential: The effect of Methergin on mutagenesis and carcinogenesis has not been determined.

Other information
Keep all medicines out of the reach of children.

Shelf-life
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
See folding box

Pack sizes
Country specific pack sizes

Manufacturer
See folding box

Information last revised
November 2011

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists